Annals of Nuclear Medicine Vol. 16, No. 1, 19–23, 2002

^{99m}Tc(V)-DMSA scintigraphy in monitoring the response of bone disease to vitamin D_3 therapy in renal osteodystrophy

Ali SARIKAYA,* Saniye SEN,** Sevim HACIMAHMUTOGLU* and Gökhan PEKINDIL***

*Departments of *Nuclear Medicine, **Internal Medicine and ***Radiology, Faculty of Medicine, Trakya University, Edirne, Turkey*

Renal osteodystrophy (ROD) is a common and serious complication for uremic patients and patients are treated with 1,25-dihydroxyvitamin D_3. The bone scanning agent ^{99m}Tc-phosphate has also been used to evaluate in ROD but it is not clear that bone scintigraphy has a role in the follow-up of treatment. In this study ^{99m}Tc(V)-DMSA scintigraphy was performed in eleven patients [age 40.7 ± 17.3 (mean ± SD) yr] with ROD before and after vitamin D_3 therapy. Images were obtained after hemodialysis performed following tracer injection to maintain normal blood levels of the radiopharmaceutical and to reduce soft tissue activity. Lumbar vertebra-to-soft tissue uptake ratios (LUR) were quantified with the planar ^{99m}Tc(V)-DMSA images. Alkaline phosphatase and parathyroid hormone levels after treatment had significantly decreased compared with pre-therapy. In all patients there was visually decreased uptake in bone structures after treatment. After treatment the mean LUR ratio was significantly lower than those of before treatment (3.59 ± 2.63 vs. 1.65 ± 0.62; $p = 0.01$). LUR values were correlated with pre-therapy alkaline phosphatase and parathyroid hormone. These findings indicate that ^{99m}Tc(V)-DMSA scintigraphy is sensitive in evaluating the response of ROD to vitamin D_3 therapy.

Key words: renal osteodystrophy, scintigraphy, ^{99m}Tc(V)-DMSA

INTRODUCTION

RENAL OSTEODYSTROPHY (ROD) is a common and serious complication for uremic patients. The importance of ROD treatment became more prominent when the number of hemodialysis patients increased tremendously in many countries and as the average life span has been prolonged. A widely used treatment in patients with ROD is vitamin D_3.

The bone scintigraphy agent ^{99m}Tc-labeled phosphate has been used to evaluate ROD[1–4] but some authors have suggested that this scan did not provide any diagnostically[5,6] and therapeutically useful information.[3,7] Recently, a case has been presented in which ^{99m}Tc(V)-DMSA (pentavalent technetium-99m dimercaptosuccinic acid) scan appeared to be more sensitive than the ^{99m}Tc-HMDP bone scan in assessing the therapeutic effect of bone disease in ROD.[3]

^{99m}Tc(V)-DMSA is a tumor-seeking agent previously reported to be effective in detecting malignant tumors and inflammatory lesions. The similarity between ^{99m}Tc(V)-DMSA and ^{99m}Tc methylene diphosphonate (^{99m}Tc-MDP) uptake in skeletal metastases and benign bone lesions, where bone metabolism is increased, has also been reported in several studies.[3,8–12] The aim of this study was to evaluate the potential of ^{99m}Tc(V)-DMSA bone scintigraphy in determining response of bone disease to vitamin D_3 therapy in ROD.

MATERIALS AND METHODS

Patients: The study received approval from the local district health authority ethics committee. Eleven patients (4 male and 7 females) aged 22–65 years (40.7 ± 17.3) were included in the study. Nine patients were on hemodialysis (HD) and two on peritoneal dialysis. All patients were ambulant. The mean duration of dialysis was 60 ± 40

Received April 23, 2001, revision accepted September 26, 2001.

For reprint contact: Ali Sarıkaya, M.D., Trakya Üniversitesi Tıp Fakültesi, Nükleer Tıp ABD, 22030, Edirne-TÜRKIYE.

E-mail: askaya@trakya.edu.tr

months (range: 32–156). All patients had renal parenchymal pathology, and some had other systemic diseases such as diabetes mellitus and systemic sclerosis were excluded.

Vitamin D_3 therapy: All patients were treated with 1,25-dihydroxyvitamin D_3 by iv injection, mean dosage 4.5 ± 1.3 μg/day (range 3–6 μg) three days a week for 6 months, after which they were treated by peroral, mean dosage 2.5 ± 3.4 μg/day (range 1–12 μg) for 4 to 10 months.

Radiology: Radiographs of the hand, pelvis, lumbar and shoulder regions were examined for subperiosteal erosions and Looser's zones.

Blood analysis: Venous blood was analyzed for calcium, phosphate, alkaline phosphatase and parathyroid hormone.

Measurement of bone mineral density (BMD): BMD of the lumbar spine was assessed by dual energy X-ray absorptiometry (DEXA) (Norland Medical Systems). BMD measurement was performed before and one-year after vitamin D_3 therapy.

Preparation of ^{99m}Tc(V)-DMSA: The home made lyophilized DMSA(III) kit contains 1.1 mg DMSA, 1.26 mg $NaHCO_3$, 0.75 mg ascorbic acid, and 0.2 mg $SnCl_2$ $2H_2O$. At the time of use, 0.2 m*l* of a 3.5% $NaHCO_3$ solution was injected into the vial. The contents were dissolved completely by gentle mixing and 2 or 3 m*l* 740 MBq ^{99m}Tc- pertechnetate was added to the vial. During preparation, the pH of the solution was checked to ensure that it was between 8.5 and 9.

Scintigraphy: ^{99m}Tc(V)-DMSA scintigraphy was performed before and 12–16 months after vitamin D_3 therapy. Scintigraphic images were obtained 4 h after iv injection of 370 MBq of ^{99m}Tc(V)-DMSA. Before scintigraphy, increased soft-tissue activity due to the absence of renal radiotracer excretion was reduced by hemodialysis.[12] Scintigraphy was performed with a large field of view gamma camera (Philiphs diagnost tomo) equipped with a low-energy, parallel-hole, high-resolution collimator, and a 20% energy windows centered on 140 keV. Images were acquired in a 128 × 128 pixel matrix for 5 min. Scintigraphic assessment was done by visual and semiquantitative interpretation. The semiquantitative analysis was performed in a blinded fashion one week later. On the pre-treatment image, the most active lumbar vertebra was selected for regions of interest (ROI) placement and the same vertebra was used for post-treatment evaluation. In some cases, contrast enhancement of images was performed to facilitate the selection of the same vertebra. Lumbar vertebra-to-soft tissue uptake ratios (LUR) were quantified with planar ^{99m}Tc(V)-DMSA images, on which were drawn a ROI of 3 × 3 pixels. No background substraction was used. Because these ratios could be affected by increases in body weight and fluid content during the therapy period, LUR was normalized to the body surface area.

Table 1 Clinical and laboratory data of patients

	Age (yr)	Sex	Duration of dialysis (mo)	ALP* (U/*l*)	PTH** (pg/m*l*)	Ca*** (mg/d*l*)	P**** (mg/d*l*)
1	61	F	32	269	345	10.8	4.5
2	53	F	22	410	729	9.1	4.8
3	22	F	96	2312	1282	10.2	6.0
4	22	M	60	300	825	9.2	8.1
5	30	F	156	764	1206	8.7	6.8
6	24	M	36	1832	252	8.7	3.0
7	40	M	59	849	1473	9.4	5.9
8	24	M	24	843	751	9.3	5.7
9	45	F	108	511	644	8.6	6.0
10	65	F	39	378	190	10.0	8.2
11	62	F	30	812	570	8.7	3.8

ALP: Alkaline phosphatase; *normal range: 225–450 U/*l*; PTH: Parathyroid hormone; **normal range: 14–72 pg/m*l*; Ca: Calcium; ***normal range: 9.0–10.7 mg/d*l*; P: Phosphate, **** normal range: 1.6–6.8 mg/d*l*

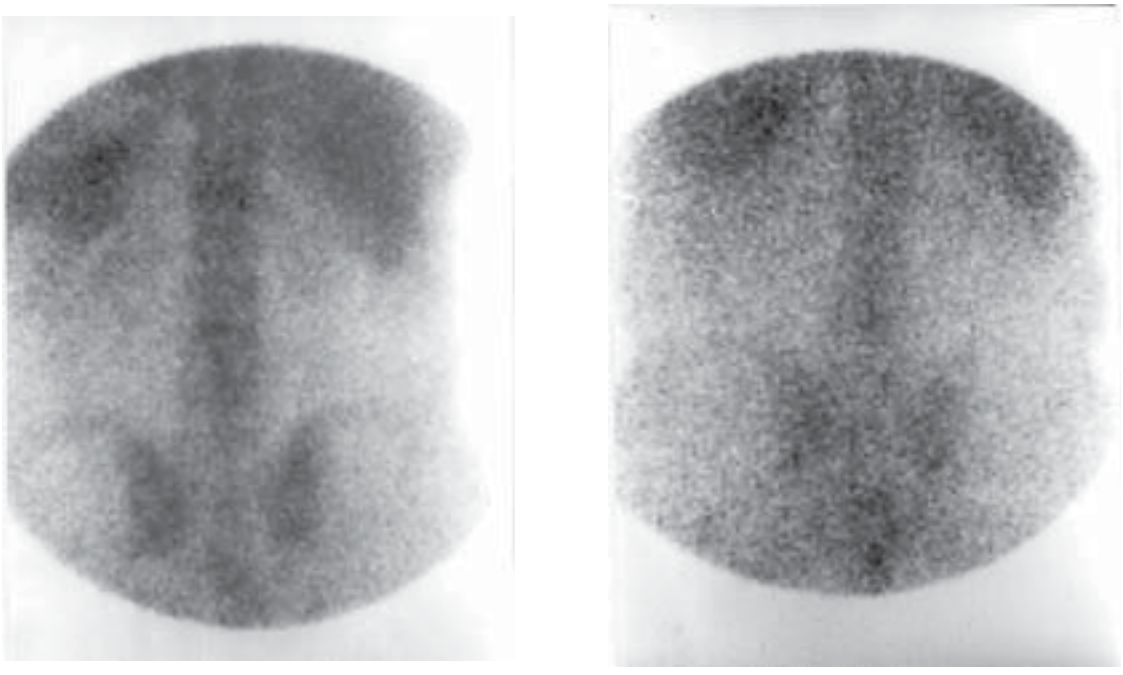
Statistical analysis: Clinical and laboratory data are expressed as the mean ± standard deviation and median value. The Wilcoxon matched test was used to analyze differences between the pre- and post-treatment segmental data, and these data are expressed as the median and range. Spearman's rank correlation coefficient was used to assess the relation between the laboratory data and LUR. A p-value <0.05 was considered significant.

RESULTS

Clinical and laboratory data of patients are summarized in Table 1. The radiographic diagnosis were osteoporosis in eight patients, osteomalacia in two patients and normal findings in one patient. Post-therapy ^{99m}Tc(V)-DMSA scan visually revealed decreased uptake in bony structures of all patients when compared to pre-therapy. The mean LUR ratio was significantly lower than those before treatment (3.59 ± 2.63 vs. 1.65 ± 0.62; p = 0.01) [Fig. 1 (case 9)-Table 2].

ALP and PTH values of after vitamin D_3 treatment were significantly lower than those before treatment (p = 0.03 and 0.01, respectively). There was no differences between pre- and post-therapy serum Ca and P levels (Table 2). LUR values were correlated with pre-therapy ALP and PTH values (r = 0.76, p = 0.009; r = 0.66, p = 0.007, respectively). There was no correlation between scintigraphic indices and serum Ca-P levels pre- and post-therapy.

BMD measurement was performed before and one-year after vitamin D_3 therapy. The mean BMD values after treatment were significantly higher than those before treatment (0.711 ± 0.102 g/cm^2 vs. 0.804 ± 0.116 g/cm^2, p = 0.04).



A B

Fig. 1 ^{99m}Tc(V)-DMSA scintigraphy on posterior lumbar area (A) before, and (B) at six months after initiation of vitamin D_3 therapy (case 9). Diffusely increased tracer uptake is noted on the regional bones (LUR: 2.66). At six months after initiation of vitamin D_3 therapy, ^{99m}Tc(V)-DMSA scintigraphy revealed decreased bone uptake compared to pre-treatment (LUR: 1.65).

Table 2 Scintigraphic indices and laboratory data before and after D_3 therapy

	LUR	ALP (U/*l*)	PTH (pg/m*l*)	Ca (mg/d*l*)	P (mg/d*l*)	BMD (g/cm^2)
Pre-therapy	3.59 ± 2.63	844 ± 654	751 ± 423	9.34 ± 0.75	5.7 ± 1.7	0.71 ± 0.10
Post-therapy	1.65 ± 0.62	339 ± 201	297 ± 238	11.2 ± 1.84	5.5 ± 1.6	0.80 ± 0.11
P-value	0.01	0.03	0.01	NS	NS	0.04

LUR: Lumbar vertebra-to-soft tissue uptake ratio; ALP: Alkaline phosphatase; PTH: Parathyroid hormone; Ca: Calcium; P: Phosphate; BMD: Bone mineral density, NS: Non-significant

DISCUSSION

Bone disorders resulting from abnormalities in mineral metabolism are common in patients with renal disease. The use of dialysis treatment has resulted in prolonged survival of patients with end stage renal failure, but some problems such as ROD have appeared. Renal osteodystrophy may present with a wide spectrum of bone lesions, ranging from high bone turnover to low bone turnover. Decreased serum calcium and 1,25-dihydroxyvitamin D synthesis and retention of phosphate are involved in the pathogenesis of high bone turnover.[14] Administration of the active vitamin D analogs, 25(OH)D_3, 1,25(OH)2D_3 and 1α(OH)D_3, to uremic patients with symptomatic bone disease is capable of reversing many of the abnormalities of divalent ion metabolism.[15,16]

A reliable diagnosis of metabolic bone disease can be obtained from a transiliac bone biopsy (BB), but this is an invasive procedure unsuited for repeated routine use. Biochemical and radiological investigations[17] are used to try to identify ROD. The biochemical findings are variable[18] and they have not proven to be specific or sensitive enough to effectively determine the potential value of a specific therapeutic regimen.[19] In the present study, ALP and PTH values after vitamin D_3 treatment were significantly lower than those before treatment. MRI is a potentially useful tool for evaluating the bone changes of renal osteodystrophy.[20,21] BMD is a useful tool for assessing bone density in patients with ROD.[2,22] BMD determines the amount of bone mass present at the time of the study, but it does not indicate the rate at which bone is lost.[23] In such a situation, there are no biochemical or radiological markers capable of totally replacing the BB in the diagnosis of ROD.

Bone scan with ^{99m}Tc-labeled phosphate has been used to diagnose ROD.[1–4] The most common appearance is of generalized increased tracer uptake throughout the skeleton, as in other metabolic disorders.[24,25] Bone scintigraphy can also help to detect the presence, severity and extent of skeletal involvement.[18] In clinical practice, quantitation of bone scanning proved disappointing in metabolic bone disorders.[26] Several methods such as the bone-to-soft tissue ratio (BSR) and 24 hr whole body retention of diphosphonate (WBR) have been proposed to measure quantitative radiophosphate uptake. Measurement of BSR for the individual is of limited value in clinical practice since there is appreciable overlap between results for individual patients and the control range.[27] Measurement of 24 hr WBR for quantitation has been shown to be helpful, but in practice is seldom performed except in research protocols.[28] In addition to this, WBR measurement is only of value in patients with normal renal function and change with age, and there are major quantitative differences between the various diphosphonates.[29,30] Kida et al.[4] observed that semiquantitative analysis, with different color scales, of whole-body bone scintigraphy was useful in assessing patients with ROD. In contrast, it has been suggested by some authors that bone scintigraphy with ^{99m}Tc-labeled phosphate did not provide any diagnostic[5,6] or therapeutically[3,7] useful information in patients with ROD. There was no consensus as to the clear usefulness of bone scintigraphy in the follow-up of ROD.

Israel et al.[31] reported that measurement of bone turnover by means of quantitative bone SPECT (QBS) is potentially useful in predicting bone loss in patients with chronic renal disease. Although QBS to measure bone turnover is a noninvasive, accurate and precise *in vivo* test to determine the rate of bone loss before a large amount of bone is lost,[31,32] its clinical use is not practical. Positron emission tomography (PET) imaging of bone with [^{18}F]fluoride ion has also been used to evaluate ROD,[33] but this is an expensive and rarely available tool for routine use.

The striking similarity between ^{99m}Tc(V)-DMSA and ^{99m}Tc-MDP uptake has been reported in many articles. A structural similarity between the technetium core in ^{99m}Tc(V)-DMSA and the orthophosphate ion has been described.[34] The tracer has been shown to bind to bone mineral analogs *in vitro*.[35] Higuchi et al.[3] recently described a patients with ROD with increased bone uptake on both ^{99m}Tc-HMDP and ^{99m}Tc(V)-DMSA scans. After vitamin D_3 pulse therapy, there was no obvious change in the ^{99m}Tc-HMDP scan but clearly decreased bone uptake was observed with ^{99m}Tc(V)-DMSA. The use of ^{99m}Tc(V)-DMSA scan has been reported in a patient's Paget's disease of bone before and after pamidronate therapy.[12] It has been shown that ^{99m}Tc(V)-DMSA scan was a useful method to achieve a therapeutic effect of pamidronate. In our study group eleven patients with ROD underwent ^{99m}Tc(V)-DMSA scan before and after vitamin D_3 therapy. ^{99m}Tc(V)-DMSA scan post-therapy visually revealed decreased tracer uptake in the skeletal bones, and the mean LUR ratio was significantly lower than those before treatment. Determination of visually different appearances in pre- and post-therapy scans is important, since use of the bone to soft tissue ratio is difficult in clinical practice.[27] According to these findings ^{99m}Tc(V)-DMSA scan is sensitive and can be used in assessing the response of ROD to vitamin D_3 therapy.

ACKNOWLEDGMENT

We are grateful to Ahmet Salan, M.D. of Department of Nuclear Medicine, Medical Faculty of Trakya University, for his excellent technical support.

REFERENCES

1. Lien JW, Wiegmann T, Rosenthall L, Kaye M. Abnormal ^{99m}Technetium-tin-pyrophosphate bone scans in chronic renal failure. *Clin Nephrol* 1976; 6: 509–512.
2. Alberts C, van der Schoot JB, Busemann-Sokole E. Bone scintigraphy and densitometry in symptomatic haemodialysis bone disease. *Eur J Nucl Med* 1981; 6: 505–509.
3. Higuchi T, Hirano T, Inoue T, Aoki J, Ueki K, Wakamatsu R, et al. Pentavalent technetium-99m-dimercaptosuccinic acid scintigraphy in renal osteodystrophy. *J Nucl Med* 1998; 39: 541–543.
4. Kida T, Narita S. A trial of semiquantitative analysis of whole body bone scintigraphy in renal osteodystrophy. *Eur J Nucl Med* 1987; 13: 36–40.
5. Dudczak R, Kletter K, Czembirek H, Derfler K, Marosi L, Salomonowitz E, et al. Radionuclide studies in chronically hemodialyzed patients. Bone scintigraphy for the evaluation and control of renal osteopathy. *Wien Klin Wochenschr* 1984; 96: 326–332.
6. Vanherweghem JL, Dhaene M, Tielemans C, Dratwa M, Verbanck P, Bergmann P, et al. Predictive value of ^{99m}Tc pyrophosphate bone scintigraphy for vitamin D trials in uraemia. *Proc Eur Dial Transplant Assoc* 1981; 18: 648–651.
7. Hodson EM, Howman-Giles RB, Evans RA, Bautovich G, Hills EE, Sherbon K, et al. The diagnosis of renal osteodystrophy: a comparison of Technetium-99m-pyrophosphate bone scintigraphy with other techniques. *Clin Nephrol* 1981; 16: 24–28.
8. Lam AS, Kettle AG, O'Doherty MS, Coakley AJ, Barrington SF, Blower PJ. Pentavalent ^{99m}Tc-DMSA imaging in patients with bone metastases. *Nucl Med Commun* 1997; 18: 907–914.
9. Akbunar AT, Orhan B, Alper E. Bone-scan-like pattern with ^{99m}Tc(V)-DMSA scintigraphy in patients with osteomalacia and primary hyperparathyroidism. *Nucl Med Commun* 2000; 21: 181–185.
10. Yuksel D, Ilgan S, Arslan N, Ugur O, Ozturk E, Bayhan H. The role of Tc-99m(V) DMSA scintigraphy in the evaluation of superscan on bone scintigraphy. *Clin Nucl Med* 2000; 2: 193–196.

11. Wulfrank DA, Schelstraete KH, Small F, Fallais CJ. Analogy between tumor uptake of technetium(V)-99m dimercaptosuccinic acid (DMSA) and technetium-99m-MDP. *Clin Nucl Med* 1989; 14: 588–593.
12. Kobayashi H, Shigeno C, Sakahara H, Yamamato T, Hosono M, Fujimoto R, et al. Three phase ^{99m}Tc(V)DMSA scintigraphy in Paget's disease: an indicator of pamidronate effect. *Brit J Radiol* 1997; 70: 1056–1059.
13. de Graaf P, Pauwels EK, Vos PH, Schicht IM, te Velde J, de Graeff J. Observations on computerized quantitative bone scintigraphy in renal osteodystrophy. *Eur J Nucl Med* 1984; 9: 419–425.
14. Cannata-Andia JB. Adynamic bone and chronic renal failure: an overview. *Am J Med Sci* 2000; 320: 81–84.
15. Sanchez CP, Goodman WG, Salusky IB. Prevention of renal osteodystrophy in predialysis patients. *Am J Med Sci* 1999; 317: 398–404.
16. Goodman WG, Coburn JW. The use of 1,25-dihydroxyvitamin D_3 in early renal failure. *Ann Rev Med* 1992; 43: 227–237.
17. Tigges S, Nance EP, Carpenter WA, Erb R. Renal osteodystrophy: imaging findings that mimic those of other diseases. *AJR* 1995; 165: 143–148.
18. McAfee JG, Reba RC, Majd M. The musculoskeletal system. In: Wagner HN, Szabo Z, Buchanan JW (eds), *Principles of Nucler Medicine*. Pennsylvania; W.B. Saunders Company, 1995: 986–1020.
19. Malluche HH, Langub MC, Monier-Faugere MC. The role of bone biopsy in clinical practice and research. *Kidney Int* 1999; 56 (Suppl 73; renal bone disease): S20–S25.
20. Ito M, Hayashi K, Noguchi M, Kitamori H. Evaluation of spinal bone changes in patients with chronic renal failure by CT and MR imaging with pathologic correlation. *Acta Radiol* 1994; 35: 291–295.
21. Olmastroni M, Seracini D, Lavoratti G, Marin E, Masi A, Vichi G. Magnetic resonance imaging of renal osteodystrophy in children. *Pediatr Radiol* 1997; 27: 865–868.
22. Arici M, Erturk H, Altun B, Usalan C, Ulusoy S, Erdem Y, et al. Bone mineral density in haemodialysis patients: a comparative study of dual-energy X-ray absorptiometry and quantitative ultrasound. *Nephrol Dial Transplant* 2000; 15: 1847–1851.
23. Peacock M. Interpretation of bone mass determinations as they relate to fracture: implications for asymptomatic primary hyperparathyroidism. *J Bone Miner Res* 1991; 6 Suppl 2: S77–82; discussion S83-4.
24. Ryan PJ, Fogelman I. Bone scintigraphy in metabolic bone disease. *Semin Nucl Med* 1997; 27: 291–305.
25. Mari C, Catafau A, Carrio I. Bone scintigraphy and metabolic disorders. *Q J Nucl Med* 1999; 43: 259–267.
26. Ryan PJ, Fogelman I. The bone scan: where are we now? *Semin Nucl Med* 1995; 25: 76–91.
27. Fogelman I, Bessent RG, Gordon D. A critical assessment of bone scan quantitation (bone to soft tissue ratios) in the diagnosis of metabolic bone disease. *Eur J Nucl Med* 1981; 6: 93–97.
28. Fogelman I, Collier BD, Brown ML. Bone scintigraphy: part 3. bone scanning in metabolic bone disease. *J Nucl Med* 1993; 22: 47–52.
29. Fogelman I, Bessent R. Age-related alterations in skeletal metabolism-24-hr whole-body retention of diphosphonate in 250 normal subjects: concise communication. *J Nucl Med* 1982; 23: 296–300.
30. Fogelman I, Pearson DW, Bessent RG, Tofe AJ, Francis MD. A comparison of skeletal uptakes of three diphosphonates by whole-body retention: concise communication. *J Nucl Med* 1981; 22: 880–883.
31. Israel O, Gips S, Hardoff R, Rudoy J, Frajewicki V, Iosilevsky G, et al. Bone loss in patients with chronic renal disease: prediction with quantitative bone scintigraphy with SPECT. *Radiology* 1995; 196: 643–646.
32. Israel O, Front D, Hardoff R, Ish-Shalom S, Jerushalmi J, Kolodny GM. *In vivo* SPECT quantitation of bone metabolism in hyperparathyroidism and thyrotoxicosis. *J Nucl Med* 1991; 32: 1157–1161.
33. Messa C, Goodman WG, Hoh CK, Choi Y, Nissenson AR, Salusky IB, et al. Bone metabolic activity measured with positron emission tomography and [^{18}F]fluoride ion in renal osteodystrophy: correlation with bone histomorphometry. *J Clin Endocrinol Metab* 1993; 77: 949–955.
34. Hirano T, Tomiyoshi K, Zhang YJ, Ishida T, Inoue T, Endo K. Preparation and clinical evaluation of technetium-99m dimercaptosuccinic acid for tumor scintigraphy. *Eur J Nucl Med* 1994; 21: 82–85.
35. Lam AS, Puncher MRB, Blower PJ. *In vitro* and *in vivo* studies with pentavalent technetium-99m-dimercaptosuccinic acid. *Eur J Nucl Med* 1996; 23: 1575–1582.